II. REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 2, 5, 7, 17-19 and 21-23 are currently amended.

Claim 42 is being added.

Claim 2 has been amended to correct a typographical error by the inclusion of parentheses around the symbol γ for consistency within the claim and the deletion of the term "and/or" with the word "and". Support for this amendment can be found on page 6, line 26 to page 7, line 2 and page 11, lines 15-19. Claim 2 also has been amended to recite that the complex prepared by the claimed method provides an "activated" complex. Support for this amendment is found on page 7, lines 6-14 and in Example II on page 15, line 29 to page 17, line 19. This amendment is made to more clearly point out and distinctly claim the scope of Applicant's invention.

Claim 5 has been amended to correct a typographical error by the inclusion of parentheses around the symbol γ, α, and β for internal claim consistency.

Claims 5, 7, 17, 18, and 21-23 have been amended to depend from claim 2 or 42.

Claims 7, 17, 18, and 21-23 have each been amended to recite that "one or more of said IKK subunit (γ) gene, or IKK subunit (α) gene or IKK subunit (β)" in place of "said IKK subunit". These amendments are made to provide proper antecedent basis of all the claim elements.

Claim 19 has been amended to recite that "one or more of said mammalian IKK subunit (γ) gene, or mammalian IKK subunit (α) gene or mammalian IKK subunit (β)" in place of "said mammalian IKK subunit". This amendment is made to provide proper antecedent basis of all the claim elements.

Support for new claim 42 can be found on page 7, line 6-14, in Example 1 and Example 2, see page 13, line 24 to page 17, line 19.

This amendment adds and changes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Applicant's amendments to the claims are made without prejudice to Applicant's right to pursue the same or similar subject matter in a related application. The claim amendments are not intended to be a dedication to the public of the subject matter of the claims as previously presented.

After amending the claims as set forth above, claims 2, 5-7, 17-19, 22, 23 and 42 are now pending in this application.

In view of the preceding amendments and remarks that follow, reconsideration and withdrawal of the rejection of the claims is respectfully requested.

35 U.S.C. § 103(a)

Claims 2, 5-7, 17-19 and 21-23 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over either Li et al. or Rothwarf et al. (Reference C27 of Applicant's PTO-1449) in view of Traincard et al. and Epinat et al.

Briefly, and without repeating the stated grounds for rejection, the Office argued that the cited art would have led a skilled artisan to reasonably expect that since yeast do not endogenously produce the IKK proteins and contain no homologs of the NF-κB signaling system, a homogenous IKK complex formed from only the heterologously introduced IKK genes would have been expected, as now claimed by Applicant.

The Office argued that the Declaration under 37 C.F.R. §1.131 to swear behind the date of the Li et al. reference was ineffective as the Declaration allegedly provided so little explanation of what the experiments of Exhibit A show (i.e., what was done in

each experiment and what does each gel shown comprise in each lane) that one cannot conclude that this is in fact shown.

With regard to the rejection over Rothwarf et al. in view of Traincard et al. and Epinat et al., the Office alleged the Applicant's arguments that the art fails to teach or suggest the production of substantially homogenous and biologically functional IKK protein complex because Rothwarf et al. 1) does not teach the autophosphorylation of the IKK complex by the IKKγ subunit; 2) does teach that the mammalian IKK complex requires post-translational processing or "activation" by protein kinases to produce biologically functional IKK complex in mammalian cells; and 3) does not teach that the active IKK complex produced in yeast could be produced by coexpression of either NIK or MEKK1, were not persuasive.

The Office rejected point 1) above on the grounds that as the autophosphorylation activity of the IKKγ subunit is allegedly an inherent function of coexpressing the α, β, and γ subunits in any eukaryotic system and thus the lack of knowledge of this activity would not have prevented a skilled artisan from selecting yeast as a suitable host as the art allegedly clearly taught how to activate the complex if it was not active upon expression. The Office also alleged that this activation is not excluded from the current claims.

The Office rejected point 2) above on the grounds that Rothwarf et al. allegedly teach the importance of phosphorylation of the IKK complex for its kinase activity and that the IKK complex produced in unstimulated cells would still have a basal level of kinase activity. As such, the Office concluded that one of skill in the art would reasonably expect that coexpression of the three subunits together in yeast would produce a complex that would have the basal level of kinase activity demonstrated by the unstimulated cells of the Rothwarf et al. and even if this in fact proved not to be the case a skilled artisan would have clearly expected that active complex could be produced by coexpression of either of NIK or MEKK1 in the yeast host.

The Office rejected point 3) above on the grounds that Rothwarf et al. allegedly teach that the IKK complex can be phosphorylated by overexpressing the NIK and MEKK1 proteins in yeast or phosphorylated *in vitro* by the same proteins to produce an active complex. The Office stated that Applicant's Declaration under 37 C.F.R. §1.132 provided no reason for believing that NIK or MEKK1 wouldn't have the same effect on the IKK complex in yeast cells that it has in mammalian cells.

Applicant respectfully traverses the rejection for the reasons which follow.

Applicant provides with this response a Supplemental Declaration under 37 C.F.R. § 1.131 by Ebrahim Zandi and Beth Schomer Miller, co-inventors of the subject application. The Supplemental Declaration establishes the conception and reduction to practice in the United States the transformation of an IKK subunit gamma (γ) gene, an IKK subunit alpha (α) and an IKK subunit beta (β) gene into yeast and the separation from that yeast a substantially homogenous, biologically functional and activated IKK protein complex prior to November 15, 2000, the online publication date of the literature article Li et al. (2001) "Role of IKKγ/NEMO in Assembly of the IκB Kinase Complex" Journal of Biological Chemistry 276(6):4494-4500. The Supplemental Declaration provided additional information to establish Applicant's prior conception and reduction to practice. In view of this Supplemental Declaration, Li et al. is not prior art to the present claims. Therefore, Applicant respectfully request removal of the Li et al. reference.

Accordingly, in an effort to further prosecution, Applicant addresses the rejection under 35 U.S.C. § 103(a) using the application of Rothwarf et al. in view of Traincard et al. and Epinat et al.

Amended claim 2 and all dependent claims thereof are directed to a method for preparing substantially homogenous, biologically functional and activated IKK protein complex by transforming a yeast with an IKK subunit gamma (γ) gene and an IKK subunit alpha (α) gene and an IKK subunit beta (β) gene, growing the yeast and separating the IKK protein complex from the yeast thereby preparing substantially

homogenous, biologically functional and activated IKK protein complex. Dependent claims 5-7, 17-19, 22 and 23 further note that: one or more of the IKK subunit genes comprise a sequence encoding a tag; one or more of the IKK subunit genes are linked to an inducible or constitutive promoter; one or more of the IKK subunit genes is a mammalian or human gene; one or more of the IKK subunit genes encode wild-type or mutated IKK subunits; the yeast is *Saccharomyces cerevisiae* or that the yeast is grown in selective liquid media. New claim 42 further includes the claim element that an IKK subunit (γ) protein encoded by the IKK subunit gamma (γ) gene solely regulates activation of the IKK protein complex. Dependent claims 5-7, 17-19 and 21-23 have been amended to depend on this newly presented claim.

Rothwarf et al. do not teach the autophosphorylation of the IKK complex regulated by the IKK subunit (γ).

Prior to proceeding with the rebuttal to the Office's rejection, Applicant would like to clarify and restate for the record that the autophosphorylation of the IKK complex is regulated by the IKK (γ) subunit. As stated by co-inventor Zandi in his Declaration under 37 C.F.R. § 1.132 filed July 17, 2008, the IKK subunit (γ) itself does not possess kinase activity. Rather it regulates the autophosphorylation of the T loop residues in the kinase domain of the IKK subunit (β). This fact is described in the subject application in Figure 4 and on page 7, lines 6-17 and in Example II on page 15, line 29 to page 17, line 19. This fact is not taught or suggested by Rothwarf et al. Applicant was the first to note that the IKK subunit (γ) provided regulation function which in turn allows for production of substantially homogenous, biologically functional and activated IKK protein complex in yeast.

As stated in Dr. Zandi's Declaration under 37 C.F.R. § 1.132 submitted with the response of July 17, 2008, Rothwarf et al. teach away from the regulation function of the IKK subunit (γ). This fact is found on page 300, left column, first paragraph wherein it states that

> "The ability of the C-terminally truncated IKK-γ mutant to inhibit IKK activation by upstream stimuli, while having only a small effect on basal kinase activity, indicates that the major function of IKK-γ may be to connect the IKK complex to upstream activators."

Thus, Rothwarf et al. actually suggests to those of skill in the art as of the effective filing date of this application that IKK (γ) does not directly regulate the autophosphorylation function of IKK (β) and that additional trans-acting proteins were necessary to provide biologically functional and activated complex in any system, including mammalian cells. At the time of the effective filing date of this application, the trans-acting proteins were believed to include TRAF2, RIP and A20. As noted in Applicant's prior response, the yeast system does not possess these proteins or any known homologues.

Rothwarf et al. do teach that the mammalian IKK complex requires post-translational processing or "activation" by protein kinases to produce biologically functional and activated IKK complex in mammalian cells

One aspect of a biologically functional IKK protein complex as produced by the claimed methods is that it is an active IKK complex capable of phosphorylating IκBα as described in the subject application in Figure 3, on page 15, lines 21-27 and on page 16, lines 18-19. The biologically functional and activated IKK complex produced in yeast by the claimed methods is capable of phosphorylating IκBα at a level that is higher than purified IKK complex from non-stimulated HeLa cells. In other words, the purified IKK complex from non-stimulated HeLa cells is not biologically functional as it only has a basal level of kinase activity. The IKK complex produced by the claimed invention is biologically functional as its capable of phosphorylating IκBα with at least an intermediate to higher level than IKK complex isolated from TNF-stimulated HeLa cells (see Declaration under 37 C.F.R. § 1.132 by Ebrahim Zandi submitted with the response of July 17, 2008).

Rothwarf et al. do not teach that the active IKK complex produced in yeast could be produced by coexpression of either NIK or MEKK1.

The Office rejected Applicant's prior distinctions and failures of the cited art on the ground Applicant's claims did not exclude the coexpression of either NIK or MEKK1. Applicant restates and incorporates by reference that as stated by Dr. Zandi,

> "Rothwarf et al., *supra*, on page 297, right column, lines 16 – 19, teaches that IKK-α/β can be phosphorylated and activated by overexpression of NIK and MEKK1 in mammalian cells, but does not teach that the IKK complex from yeast of the present application containing IKKα, IKKβ, and IKKγ can be activated by NIK or MEKK1 in yeast systems. Rothwarf et al. also teaches that the physiological role of NIK and MEKK1 in IKK activation by pro-inflammatory cytokines is not clear."

Thus, as stated by Dr. Zandi, this statement shows that the authors were uncertain as to the role of NIK or MEKK1 in activating IKK proteins. Therefore, Rothwarf et al. does not teach nor would one of ordinary skill in the art from the teachings of Rothwarf et al. expect that any IKK complex produced in yeast would be activated even with coexpression of either NIK or MEKK1 (see Response and Reply filed on July 17, 2008, regarding production of active IKK complex by coexpression of either NIK or MEKK1 found on page 9).

Without conceding to the correctness of the Office's position and in a sincere effort to further prosecution, Applicant presents new claim 42. New claim 42 explicitly notes that an IKK subunit (γ) protein encoded by the IKK subunit gamma (γ) gene solely regulates activation of the IKK protein complex. Applicant presents this claim and the claims which are now made dependent upon it as non-obvious over the cited art of record. The cited art, alone or in combination with each other, fails to teach or suggest all the elements of the claimed method, i.e. an IKK subunit (γ) protein encoded by the IKK subunit gamma (γ) gene solely regulates activation of the IKK protein complex. Moreover, based on the combined teachings with the knowledge of one of skill in the art as of the effective filing date of the application, an expectation of success was lacking, as it was believed, as Rothwarf et al. states, that IKK complex required

post-translational processing or "activation" by trans-acting protein kinases to produce biologically functional IKK complex, such as TRAF2, RIP and A20. Yeast do not posses these proteins or any known homologues.

The Supreme Court clarified the factual inquiry and legal standard for obviousness under 35 U.S.C. § 103 in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). In *KSR*, the Supreme Court stated that if the elements of the alleged invention are known in the technical art, it is not necessary that the references expressly teach or direct the skilled artisan to combine them in the manner of the claimed invention. A claimed invention will fail the standard of 35 U.S.C. § 103 if a person of skill in the art would be motivated to combine the elements of the prior art to solve a need or problem known in the field and addressed by the patent claim. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has a good reason to pursue the known options within his or her technical grasp. If the pursuance of the known options leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

In this case, the combined teachings of the prior art fail to provide the elements of the claimed invention and would not lead to a finite number of identified, predictable solutions with anticipated success. Indeed, one of skill in the art would have had a reasonable expectation of failure since the yeast system does not posses a necessary element required for the production of biologically functional and activated IKK complex. For these reasons, and in view of the evidence of record, the rejection is improper and Applicant respectfully requests its withdrawal.

III. CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: February 13, 2009

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